The Effect of Stereoelectronic Control in Proton Removal from 4-t-Butylcyclohexanone

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Summary Evidence is presented to show that the axial α-hydrogens of 4-t-butylcyclohexanone undergo base-catalysed hydrogen-deuterium exchange at a faster rate than the equatorial α-hydrogens.

The theory of stereoelectronic control, first proposed by Corey and Sneen[1] to explain the preferential removal of the 6β-axial proton over the 6α-equatorial proton in 3β-acetoxycholestan-7-one, has been used extensively in organic chemistry to explain many experimental observations.[2] However, in a recent report concerning base-catalysed hydrogen-deuterium exchange of cyclohexanone and some 4,4-disubstituted derivatives, 4,4-diphenyl-, 4,4-dimethyl-, and 4-methyl-4-phenyl-cyclohexanone, Bordwell[3] and his co-workers questioned the importance of stereoelectronic control in influencing the rate of proton exchange, since all of the 4,4-disubstituted cyclohexanones afforded exchange rates close to that of cyclohexanone itself.

Table. Second-order rate constants of NaOD-catalysed deuterium exchange in [$^2H_6$]dimethylsulphoxide–D_2O at 37·0° (k_2/l mol^{-1} s^{-1})[a,b]

Ketone	Axial	Equatorial	Ax : Eq
Cyclohexanone	$3{\cdot}6 \times 10^{-1}$		
4-t-Butylcyclohexanone	$11{\cdot}0 \times 10^{-1}$	$2{\cdot}0 \times 10^{-1}$	5·5

[a] The second-order rate constants were obtained by dividing the experimentally determined pseudo first-order rate constants by the base concentration. [b] Average of 2–4 runs; maximum deviations of ±10%.

The above results prompt us to report our findings concerning the base-catalysed hydrogen-deuterium exchange of cyclohexanone and 4-t-butylcyclohexanone which seem to be in good agreement with the theory of stereoelectronic control and to contradict Bordwell's conclusions.

In a preparative experiment 0·5 g 4-t-butylcyclohexanone was dissolved in 12 ml dioxan, 4 ml 0·042M NaOD–D_2O were added and the reaction mixture was stirred for 30 min at room temperature. It was then neutralized with a few drops of aqueous hydrochloric acid and quickly poured into 200 ml aqueous saturated solution of sodium chloride. The ketone which precipitated immediately, was collected by filtration, dried and its n.m.r. spectrum recorded in CCl_4, in the presence of Eu(THD)$_3$.† The spectrum showed one hydrogen remaining in the equatorial position and 0·21 hydrogens remaining in the axial position. Under these conditions, the doublet at δ 7·66 due to the equatorial hydrogens† had collapsed to a singlet.

These results show that the axial protons at C-2 in 4-t-butylcyclohexanone exchanged faster than the corresponding equatorial protons, in line with the predictions of the theory of stereoelectronic control.‡

Further support of the theory was obtained *via* kinetic experiments involving cyclohexanone and 4-t-butylcyclohexanone. The rate of base-catalysed hydrogen-deuterium exchange of these two ketones in [$^2H_6$]dimethylsulphoxide–D_2O and NaOD were followed by a known n.m.r. method.[4]§ The conditions of the reaction were such that first-order kinetics in base were maintained. An excess of ketone was

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† N.m.r. spectrum of 4-t-butylcyclohexanone (0·05 g) with 0·10 g Eu(THD)$_3$ in 0·50 ml of CCl_4 [δ 0·32 (s, 9H, 4-t-butyl), 2·7 (m, 5H, H's at C-3, C-4, and C-5), 6·64 (m, 2H, axial H's at C-2 and C-6) and 7·66 (d, 2H, equatorial H's at C-2 and C-6 $J_{ax,eq}$ 14 Hz)]. These assignments are in agreement with the work of J. K. M. Sanders and D. H. Williams, *J. Amer. Chem. Soc.*, 1971, **93**, 641, who first reported the effect of Eu(THD)$_3$ on the n.m.r. spectra of lone pair bearing organic compounds.

‡ As one of the referees pointed out the observations described herein result from the preferred direction of deuterium capture by the 4-t-butylcyclohexanone enolate anion, and only by application of the principle of microscopic reversibility can these results be extended to the preferred direction of proton abstraction.

§ The extent of deuterium exchange was determined by the ratio of the remaining α-hydrogens to an internal standard, such as the 4-t-butyl group in 4-t-butylcyclohexanone, or the six hydrogens at C-3, C-4 and C-5 in cyclohexanone.

maintained (10: 1) and sufficient D_2O was used to ensure rapid deuteration. The data were treated in a least squares analysis for log [H] removed *vs* time. Second-order rate constants (Table) were obtained by dividing the pseudo first-order rate constants by the base concentration, $k_2 = k_{obs}/[B]$.

Under these conditions, cyclohexanone showed one rate of exchange for all of its α-hydrogens, while 4-t-butylcyclohexanone showed two rates (Table).

In accordance with the results of the preparative experiment described earlier, the faster rate of 4-t-butylcyclohexanone was assigned to the axial α-hydrogens while the slower rate was attributed to the equatorial α-hydrogens.

The results are again in good agreement with the theory of stereoelectronic control‡ Although the ratio of axial: equatorial hydrogens of 5·5 (Table) is somewhat less than that predicted by Corey and Sneen in their original publication[1] it is nevertheless still significant.

Exactly why the 4,4-substituted cyclohexanones studied by Bordwell[3] and his co-workers did not display a slower rate of hydrogen-deuterium exchange relative to cyclohexanone is not entirely clear, although a number of contributing factors may be cited. However, in view of the experimental results outlined lack of stereoelectronic control does not appear to be one of them.

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